Direct Healthcare Professional Communication

25 July 2017

Shortage of Trisenox® (arsenic trixode, 1 mg/ml concentrate for solution for infusion): replacement with imported arsenic trioxide injection 1 mg/ml (Phenasen) during supply shortage

Dear Healthcare Professional:

Teva B.V. (marketing authorisation holder of Trisenox) in agreement with the European Medicines Agency and MHRA would like to inform you of the following:

Summary

- **Manufacturing issues with Trisenox are anticipated to lead to a shortage in EU markets by mid/late August 2017 until normal supply can be resumed. The safety and efficacy of the product currently on the market is not affected by these manufacturing issues.**
- **In order to ensure supply continuity, Teva has decided to import in the EU an equivalent injection containing 1 mg/ml of arsenic trioxide (known as Phenasen by Phebra Pty Ltd) which is a licensed product from Australia but will be classified as an unlicensed product in the UK.**
- **Phenasen and Trisenox contain the same active ingredient, arsenic trioxide, in the same total concentration: 10 mg of arsenic trioxide in 10 ml. Whereas Trisenox is available as an ampoule Phenasen is available as a vial.**

Background

Trisenox (arsenic trioxide) is indicated for induction of remission, and consolidation in adult patients with:

- Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all-trans-retinoic acid (ATRA)
- Relapsed/refractory acute promyelocytic leukaemia (APL) (previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.

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Teva recently changed the manufacturer of Trisenox, which was approved in the EU on 5th May 2017. However, there have been some manufacturing issues with the new manufacturer, who is working diligently to rectify the situation. During the visual inspection of some batches of Trisenox, semi-transparent solutions were observed within the ampoules. An investigation is ongoing to identify the root cause and the necessary corrective and preventive actions. No batches from the new supplier will be released on the EU market until a satisfactory outcome of the investigation has been completed. However, Trisenox ampoules currently on the market are not affected by these manufacturing issues.

Currently, the European markets are supplied with Trisenox ampoules taken from the stock of the previously registered manufacturer. However, this stock is running low and although Teva is making every effort to re-distribute stocks across EU markets, stocks are anticipated to run out by mid/late August 2017. In order to ensure supply continuity, Teva has decided to import in the EU an equivalent injection containing 1 mg/ml of arsenic trioxide (known as Phenasen by Phebra Pty Ltd) from Australia.

Both Phenasen and Trisenox, contain the same active ingredient, arsenic trioxide, in the same total concentration: 10 mg of arsenic trioxide in 10 ml. Please note that whereas Trisenox is available as an ampoule Phenasen is available as a vial

Company contact point

If you have any additional questions about product availability or ordering of Trisenox® Injection, please contact Teva UK Customer Services on 0800 590 502 or email: customer.services@tevauk.com

Call for questions

Healthcare providers and patients should contact the Teva UK medical information department on 0207 540 7117 or email: medinfo@tevauk.com if you have any questions about:

- reporting quality problems and all adverse events in patients taking Trisenox Injection
- the information contained in this letter or the safe and effective use of Trisenox Injection.

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme. Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason.

It is easiest and quickest to report ADRs online via the Yellow Cards website – https://yellowcard.mhra.gov.uk/

Alternatively, prepaid Yellow Cards for reporting are available:

- by writing to FREEPOST YELLOW CARD (no other address details necessary)
- by emailing yellowcard@mhra.gov.uk
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line: 0800- 731-6789
- or by downloading and printing a form

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Adverse events should also be reported to Teva UK Limited at: www.tevauk.com

Annexes

Trisenox and Phenasen (arsenic trioxide) Injection: Product Information differences

Yours Sincerely,

Dr Ewan Walters
Senior Director Medical Affairs UK & Ireland
Teva UK Limited

Annexe

Amsterdam, XX July 2017

IMPORTANT DRUG INFORMATION

Subject: Trisenox and Phenasen (arsenic trioxide) 1 mg/ml concentrate for solution for infusion: Product Information differences

PRODUCT INFORMATION: Phenasen

Each 10 ml contains 10 mg arsenic trioxide as the active ingredient. It also contains sodium hydroxide and water for injections. Hydrochloric acid is added for pH adjustment. It is a sterile solution for single use and contains no antimicrobial preservative. The pH range of Phenasen is 5.0-8.5. Phenasen must be diluted before use. Phenasen (Arsenic Trioxide Injection 10 mg/10 ml) is presented in 10 ml vials in cartons of 10. Store below 30ºC.

THERAPEUTIC INDICATIONS

- For the induction of remission and consolidation in patients with acute promyelocytic leukaemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.

- For the induction of remission and consolidation in patients with previously untreated acute promyelocytic leukaemia (APL) in combination with *all-trans* retinoic acid (ATRA) and/or chemotherapy and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression (the indication is not limited to low-intermediate risk APL patients).

DOSAGE AND ADMINISTRATION

Method of administration

0.15 mg/kg/day diluted with 100 - 250 ml of 5% glucose injection or 0.9% sodium chloride injection and administered intravenously (iv) over two hours.

Once diluted the solution should be used as soon as possible. It is a sterile solution for single use and contains no antimicrobial preservative. If storage is necessary the prepared solution should be refrigerated between 2°C and 8°C and stored for no longer than 24 hours before discarding.

Dosage

Newly diagnosed APL patients are divided in:

High risk APL patients: ATO in combination with ATRA + chemotherapy (this indication is not included in Trisenox SmPC).

Low-to intermediate risk APL patients: ATO combination with ATRA.

- Induction: 0.15 mg/kg/day from day 1 until haematological CR or for a maximum of 60 days. If no hematological CR is achieved by day 60 discontinue treatment. (the schedule and dose is the same as in Trisenox SmPC).

- Consolidation: 0.15 mg/kg/day 5 days per week. 4 weeks on and 4 weeks off, for a total of 4 cycles (the schedule and dose is the same as in the Trisenox SmPC).

Relapsed/refractory acute promyelocytic leukaemia (APL)

- Induction Treatment: for induction, a daily infusion of 0.15 mg/kg/day is continued until bone marrow remission is obtained. If bone marrow remission is not obtained by day 60, dosing must be discontinued (this schedule is slightly different compared with Trisenox SmPC, the dose is the same).

- Consolidation Treatment: an additional course beginning consolidation of treatment may begin 3-4 weeks after completion of the induction cycle. The dose is the same as for induction, except that 25 daily doses over a period of up to 5 weeks are given (the schedule and dose is the same as in the Trisenox SmPC).

PRODUCT INFORMATION: Trisenox

Trisenox 1 mg/ml concentrate for solution for infusion. One ml of Trisenox contains 1 mg of arsenic trioxide. Nature and contents of container: Type I borosilicate glass ampoule containing 10 ml of concentrate. Each pack contains 10 ampoules. List of excipients: Sodium hydroxide, Hydrochloric acid (as pH adjuster), Water for injections. Special precautions for storage: Do not freeze.

THERAPEUTIC INDICATIONS

It is indicated for induction of remission, and consolidation in adult patients with:

• Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL) (white blood cell count, ≤ 10 x 10^3/µl) in combination with all-trans-retinoic acid (ATRA).

• Relapsed/refractory acute promyelocytic leukaemia (APL)(Previous treatment should have included a retinoid and chemotherapy) characterised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid-Receptor-alpha (PML/RAR-alpha) gene.

The response rate of other acute myelogenous leukaemia subtypes to arsenic trioxide has not been examined.

DOSAGE AND ADMINISTRATION

Method of administration

Trisenox must be diluted with 100 to 250 ml of glucose 50 mg/ml (5%) solution for injection or sodium chloride 9 mg/ml (0.9%) solution for injection immediately after withdrawal from the ampoule. It is for single use only, and any unused portions of each ampoule must be discarded properly. Do not save any unused portions for later administration.

After dilution in intravenous solutions, Trisenox is chemically and physically stable for 24 hours at 15°C-30°C and 48 hours at refrigerated (2°C-8°C) temperatures. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Dosage

Newly diagnosed low-to-intermediate risk acute promyelocytic leukaemia (APL):

- Induction treatment schedule: Trisenox must be administered intravenously at a dose of 0.15 mg/kg/day, given daily until complete remission is achieved. If complete remission has not occurred by day 60, dosing must be discontinue
- Consolidation schedule: Trisenox must be administered intravenously at a dose of 0.15 mg/kg/day, 5 days per week. Treatment should be continued for 4 weeks on and 4 weeks off, for a total of 4 cycles.

Relapsed/refractory acute promyelocytic leukaemia (APL)

- Induction treatment schedule: Trisenox must be administered intravenously at a fixed dose of 0.15 mg/kg/day given daily until complete remission is achieved (less than 5% blasts present in cellular bone marrow with no evidence of leukaemic cells). If complete remission has not occurred by day 50, dosing must be discontinued.
- Consolidation schedule: Consolidation treatment must begin 3 to 4 weeks after completion of induction therapy. Trisenox is to be administered intravenously at a dose of 0.15 mg/kg/day for 25 doses given 5 days per week, followed by 2 days interruption, repeated for 5 weeks.

COMMENT:

Phenasen and Trisenox: both products contain arsenic trioxide as the active ingredient in the same concentration: 10 ml contains 10 mg arsenic trioxide, however:

- Phenasen presentation is a vial
- Trisenox presentation is an ampoule

INDICATION:
newly diagnosed APL patient:

- Phenasen: the indication is not limited to low-intermediate risk APL patients
- Trisenox: the indication is limited only in low-intermediate risk APL patients

Moreover, in newly diagnosed APL patient, Phenasen may be given in combination with all-trans-retinoic acid (ATRA) and/or chemotherapy, depends on the risk stratification. Instead in Trisenox SmPC only in combination with ATRA in low-to-intermediate risk APL patients.

SCHEDULE AND DOSAGE:

- Phenasen: there is a different schedule for the newly diagnosed APL patients based on the risk stratification:
    - High risk (white blood cell count, ≥ 10 x 10^9/L) include the combination of ATRA + chemotherapy + ATO. This indication is not included in the Trisenox SmPC.
    - Low-to intermediate risk (white blood cell count, ≤ 10 x 10^9/L) include ATRA + ATO. The schedule and dose of low-to intermediate risk APL patients is the same in the Phenasen and Trisenox product information.
- Phenasen: there is a different schedule on the relapse/refractory APL patients:
    - Induction is 60 days in Phenasen product information, it is 50 days in Trisenox SmPC
    - Consolidation: the schedule and dose is the same in the Phenasen and Trisenox product information.
- Dose Modification due to treatment related adverse event (grade 3 or greater, based on the National Cancer Institute Common Toxicity Criteria): Patients must resume treatment only after resolution of the toxic event or after recovery to baseline status of the abnormality that prompted the interruption. In such cases, treatment must resume at 50% of the preceding daily dose. However there is a small difference on time of (re)-escalation of 100% of the dosage:
    - Phenasen: If the toxic event does not recur within 3 days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100% of the original dose. Patients who experience a recurrence of toxicity must be removed from treatment.

- Trisenox: if the toxic event does not recur within 7 days of restarting treatment at the reduced dose, the daily dose can be escalated back to 100% of the original dose. Patients who experience a recurrence of toxicity must be removed from treatment.

- Moreover for symptoms related to QT prolongation, in the Trisenox SmPC. After recovery, treatment should be resumed at 50 % of the preceding daily dose. If QTc prolongation does not recur within 7 days of restarting treatment at the reduced dose, treatment with Trisenox can be resumed at 0.11 mg/kg body weight per day for a second week. The daily dose can be escalated back to 100% of the original dose if no prolongation occurs. This specific (re)-dose escalation in two steps in patients with syncope and irregular heartbeat cease and QT prolongation is not mentioned in the Phenasen product Information.

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